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TRANSMITTAL OF APPEAL BRIEF

Docket No.
62053CIP(51588)

In re Application of: Mark C. Poznansky et al.

Application No.	Filing Date	Examiner	Group Art Unit
10/002,854-Conf. #3669	November 1, 2001	L. B. Lankford	1651

Invention: CAR RECEPTOR AS A MEDIATOR OF MIGRATORY CELL CHEMOTAXIS AND/OR CHEMOKINESIS

TO THE COMMISSIONER OF PATENTS:

Transmitted herewith is the Appeal Brief in this application, with respect to the Notice of Appeal filed: July 29, 2005 .

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Dated: February 27, 2006

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No. : 10/002,854 Confirmation No 3669
Appellants : Poznansky, Mark C., et al.
Filed : November 1, 2001
TC/A.U. : 1651
Examiner : Lankford, Jr., Leon B.

Docket No. : 62053CIP(51588)
Customer No. : 21874
For: CaR Receptor as a mediator of migratory cell chemotaxis and/or chemokinesis

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APPEAL BRIEF

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Sir:

This Brief on Appeal is submitted pursuant to the Notice of Appeal received in the U.S Patent and Trademark Office on August 1, 2005, and in support of the appeal from the final rejection(s) set forth in the Office Action mailed on March 30, 2005. The fee for filing a brief in support of an appeal and a 5 month extension of time are enclosed.

(1) The Real Party of Interest

The real party of interest in this appeal is The Brigham and Women's Hospital Inc., by virtue of Assignment by Edward M. Brown recorded on March 29, 2002 at Reel 012760 and Frame 0020 and The General Hospital Corporation by virtue of the Assignment by David T. Scadden recorded on March 29, 2002 at Reel 012760 and Frame

0088 and The General Hospital Corporation by virtue of the Assignment by Ivona T. Olszak recorded on March 29, 2002 at Reel 012760 and Frame 0088 and The General Hospital Corporation by virtue of the Assignment by Mark C. Poznansky recorded on March 29, 2002 Reel 012760 and Frame 0088.

(2) Related Appeals and Interferences

There are no appeals or interferences related to this application.

(3) Status of the Claims

Claims 10, 93-98, 100 and 105 are pending, finally rejected and appealed. Claims 2-9 and 11-84 were previously cancelled. Claims 1, 85-92, 99 and 101-104 were finally rejected but are not appealed. The supplemental amendment filed on February 27, 2006 requests cancellation of these claims.

(4) Status of the Amendments

A Reply After Final Rejection was filed on June 30, 2005. It is believed that the amendment was entered. A supplemental amendment after the Final Office Action was filed on February 27, 2006 and it is believed that the amendment will be entered as it clearly reduces issues on appeal. However, as of the date of this brief, Appellants have not been advised of its entry.

(5) Summary of the claimed subject matter

The invention relates to methods and compositions for modulating movement of eukaryotic cells with migratory capacity. See the abstract. More specifically the invention relates to methods and compositions for modulating movement of calcium-sensing receptor (CaR) expressing cells of hematopoietic, neural, epithelial, endothelial, or mesenchymal origin in a specific site in a subject. The foregoing are useful inter alia in the treatment of conditions characterized by a need to modulate migratory cell movement associated with specific sites in a subject. Specific sites include sites of inflammation and modulation of migratory cell movement is movement away from an agent source, or repulsion. The invention also relates to methods for manipulating hematopoietic

progenitor cells and related products. In particular the invention includes methods and products for using CaR-related compositions to enhance mobilization of hematopoietic progenitor cells, to improve the efficiency of targeting cells to the bone marrow and/or to modulate hematopoietic progenitor cell function.

(6) Ground of rejection to be reviewed

The sole issue on appeal is whether the Examiner has established a *prima facie* case of obviousness of one or all claims.

(7) Argument

(a) The Rejection

In the Advisory Action dated December 8, 2005, the Examiner maintains the finality of the rejection made in the Final Office Action dated March 30, 2005. In the Final Office Action, the Examiner maintained the rejection of claims 1, 10 and 85-105, under 35 USC 103(a) as being unpatentable over Yamaguchi et al, (*J. Bone Min. Research* Vol. 10(13)1530, 1998) ("Yamaguchi").

(b) The Rebuttal

In the Final Office Action, the Examiner alleges that Yamaguchi teaches that calcium-sensing receptor (CaR) agonists stimulate chemotaxis of cells that have the CaR. While admitting that the reference does not teach administration of an agonist (or antagonists) to a subject, the Action takes the position that it would have been obvious to administer an agonist to a subject in order to facilitate migration of any known calcium-sensing receptor expressing cell with the reasonable expectation that the cells would migrate to the concentration of the agonists as shown *in vitro* by Yamaguchi. The Action further asserts that "if agonists will effect migration, then antagonists will as well" (page 2, paragraph 3 of the Action). Finally, the Examiner concludes that the claimed invention is *prima facie* obvious to one of ordinary skill in the art "especially in the absence of evidence to the contrary."

Appellants respectfully disagree. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation,

either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Furthermore, the teachings or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The presently claimed invention comprises methods of **inhibiting migration** of calcium-sensing receptor expressing **hematopoietic cells** to a specific site in a subject, comprising **locally administering to a specific site in a subject** in need of such treatment a calcium-sensing receptor antagonist in an amount effective to inhibit migration of calcium-sensing receptor expressing hematopoietic cells to the specific site in the subject (emphasis added).

It is well known that "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). Consequently, a comparison of Yamaguchi to the present invention supports Appellants' position that Yamaguchi does not teach or suggest all the claim limitations of the present invention.

The Yamaguchi Reference

Firstly, the reference does not teach **inhibition of migration** by administering an antagonist. The Examiner assumes, without any support, that the person of ordinary skill in the art would conclude that, given the ability to induce chemotaxis of a particular cell in the presence of calcium *in vitro*, inhibition of chemotaxis or activating fugetaxis *in vivo* would be obvious. This assumption is completely unsupported by any evidence and is improper.

In no manner does the Yamaguchi reference suggest that **hematopoietic cells** expressing the calcium-sensing receptor (CaR) can be stimulated *in vivo* to migrate, or not to migrate, to designated sites when contacted *in situ* with a non-Ca^{2+} agonist, or a calcium receptor antagonist. Appellants can identify neither teaching nor suggestion to

enhance calcium-sensing receptor expressing cell migration to a specific site *in vivo*, whether by analogy to Yamaguchi's *in vitro* mouse clonal cell study model, or from any teaching or suggestion taken from a reading of the entire reference.

Appellants have studied the Yamaguchi paper and believe that it teaches the use of MC3T3-E1 cells as a potential model for examining the process of **osteoblastic** development *in vitro* (please refer to Discussion, page 1535, second paragraph). A reading of the entire publication further supports Appellants' understanding of the goal of the Yamaguchi study (including results and conclusions) as directed to developing an *in vitro* model for investigating bone formation. The authors state (page 1537, col 2, last paragraph):

> In this study, using MC3T3-E1 cells as a model, we show that osteoblasts, which play an important role in bone remodeling within the skeleton, express both CaR protein and mRNA. Our results suggest that this receptor may be involved in important physiological responses of these cells, such as chemotaxis and proliferation after stimulation by Ca^{2+}. These events are observed at the beginning of the bone formation phase of skeletal remodeling in vivo, suggesting that the CaR could potentially play a key role in the function of bone cells within the bone/marrow microenvironment.

The lack of explicit or implicit teaching of the use of agonists (or antagonists) to control cell migration is illustrated in Yamaguchi's statement (page 1537, first paragraph, last sentence): "Thus, additional studies are needed to document further causal relationships between expression of the CaR, its signal transduction pathways and the control of chemotaxis and cell proliferation by CaR agonists in this osteoblastic cell line."

They speculated that the MC3T3-E1 cells **could** be a model for osteoblastic cells and because they expressed the calcium-sensing receptor for up to 20 days in culture that **perhaps** *in vivo* cells could express the calcium-sensing receptor throughout their differentiation, based in part on the **possibility** that "...a calcium-sensing mechanism is present in these osteoblastic cells and is involved in their migration and proliferation." (page 1536, col 1, first paragraph, line 12-14; emphasis added).

Interestingly, Yamaguchi indicated the need for "additional studies ...to document further causal relationships between expression of the calcium-sensing receptor, its signal transduction pathways and the control of chemotaxis and cell proliferation by the

calcium-sensing receptor agonists in this osteoblastic cell line." Please see column 1, last paragraph bridging over to column 2 on page 1537 through the first paragraph.

Accordingly, these statements direct one of skill in the art to study Yamaguchi's cell culture model of osteoblast cells in order to determine the responses of these particular cells. There is no implicit teaching of how to use knowledge of the effects of high concentration of Ca^{2+}, Gd^{3+} or neomycin sulfate on these cells to enhance or inhibit chemotactic or fugetactic or any chemokinetic activity *in vivo* nor the desirability to do so.

Secondly, the reference does not teach modulating migration of the class of **hematopoietic cells**, as claimed herein, *in vivo* or the desirability to do so. In this case, predictability of the Yamaguchi study with respect to osteoblastic cells alone is speculative, let alone any translation of effects to altering the migratory capacity of the hematopoietic cells of the present invention. Yamaguchi provides no guidance for *in vivo* use, and the osteoblast-like "model" showed that it was difficult to identify a calcium-sensing receptor in MC3T3-E1 cells derived from mouse calvaria and having an osteoblast-like phenotype. There is no guidance or suggestion to administer an agonist or antagonist to a specific site in order to prevent or induce migration of calcium-sensing receptor cells of the class of **hematopoietic cells** to that site.

Finally, appellants note that there is no reasonable expectation that the effects observed MC3T3-E1 cells cultured *in vitro* would be translated to a useful ***in vivo*** outcome. Thus, there is no motivation to **locally administer** a compound to a subject, as required by the claims. Indeed, the law mandates that the Examiner establish that the art teach or suggest the desirability to make a proposed modification. In this case, there is no motivation to move the teachings of Yamaguchi *in vivo*. Yamaguchi, at best, is suggesting that a particular osteoblastic clonal cell line is useful to study bone formation. This simply cannot be translated into an *in vivo* model. Applying the method of the present invention to Yamaguchi, whereby an antagonist is administered to a subject inhibiting osteoblastic cell migration to induce bone formation, effectively renders the Yamaguchi model unsatisfactory for its intended purpose, i.e. the system developed by Yamaguchi becomes useless as a potential model for examining the process of

osteoblastic development *in vitro* and inhibiting the migration of bone forming cells (osteoblasts) is contrary to the bone formation process.

The law is clear on the connection between inoperability of a reference and establishment of *prima facie* obviousness. To this end, the court has stated "an applicant may rebut a *prima facie* case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect" and that if a reference taken in combination (or alone as is the case here) would produce a seemingly inoperative device, such references are considered to teach away from the combination and cannot serve as predicates for a prima facie case of obviousness. McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1354, 60 USPQ 2d 1001 (Fed. Cir. 2001); see also In re Gurley, 27 F.3d 551, 553, 31 USPQ 2d 1130, 1132 (Fed. Cir. 1994); In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984); In re Sponnoble, 56 CCPA 823, 405 F.2d 578, 587, 160 USPQ 237, 244 (CCPA 1969).

In addition, applying the Yamaguchi method to the present invention would change the principle of operation of the present invention and the law on this point is likewise well settled. If a proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

Yamaguchi does not amount to a teaching of the local administration of an **antagonist** to a subject whereby migration of **hematopoietic cells** expressing the calcium-sensing receptor is **inhibited** to effect the treatment of inflammatory conditions. Where, as here, there is no real utility taught or suggested by the prior art, there is no motivation to modify. Thus, even if it were true that one of ordinary skill in the art would expect the *in vitro* results observed to translate *in vivo*, the reference does not teach a reason why one should undertake such modifications or the modifications necessary to achieve the claimed invention.

In the Advisory Action, the Examiner states that the amendment submitted after the Final Office Action, limiting the claims to hematopoietic cells, does not place the application in condition for allowance because "Appellant argues that there is no reasonable expectation of success to extrapolate the Yamaguchi reference teachings to

the *in vivo* effect on hematopoietic cells however it is unclear where applicant has demonstrated this and applicant would seem to depend on a like extrapolation with only a suggestion of *in vivo* use."

In fact, the application, as originally filed, contains *in vitro* **and** *in vivo* data and evidence directed to the impact of compounds on hematopoietic cells, in particular monocytes, as well as *in vitro* data on peripheral blood cells and hematopoietic progenitor cells (all hematopoietic cells). See Example 1, ¶¶ 137-141 of the present invention. Thus, the Examiner's reason for maintaining the rejection is technically flawed. Indeed, the Interview Summary Record of July 27, 2005 invited a subsequent interview, presumably to discuss the merits of the statements in the Advisory Action. However, because of the exceedingly lateness of advising the Appellants of the grounds for maintaining the rejections, Appellants have been procedurally denied the opportunity to correct the technical misunderstanding.

Furthermore, the statement establishes that the Examiner misunderstood the Appellants' argument. Appellants are not arguing that *in vivo* data is required to establish a reasonable expectation of success in this technical area. Where, as here, the reference is directed to developing an *in vitro* cell model for studying bone formation using calcium (a receptor agonist) and an osteoblastic clonal cell line, the reference does not teach, with a reasonable expectation of success, the local administration of a receptor antagonist to inhibit hematopoietic cell migration *in vivo* to treat a disease or condition in a subject.

Examiner notes in the Final Office Action that "enhancement of migration" is not a strenuous requirement given the teachings of the prior art regarding the effects of chemotaxis. While Appellants respectfully disagree, the present appeal, directed only to the claims encompassing inhibition of migration renders this argument moot.

Appellants conclude that a fair reading of Yamaguchi indicates to one of skill in the art that there was no suggestion that one could inhibit migration of calcium-sensing receptor expressing hematopoietic cells in a subject by locally administering to a specific site in a subject in need of such treatment a calcium-sensing receptor antagonist in an amount effective to inhibit migration of calcium-sensing receptor expressing hematopoietic cells to the specific site in the subject.

In view of the above arguments, Appellants submit that they have rebutted any *prima facie* case of obviousness that the Examiner may have established and respectfully request that the rejection under 35 U.S.C. §103 over Yamaguchi be withdrawn and claims 10, 93-98, 100 and 105 be moved to allowance.

Although Appellants' remarks above are limited to rebuttal of the alleged *prima facie* case of obviousness over Yamaguchi, Appellants continue to maintain that the Examiner has not, in fact, established a *prima facie* case of obviousness.

(c) Claim Groupings

The pending claims are 10, 93-98, 100 and 105.

Claim 10

If the Examiner finds Claim 10 allowable then all claims are allowable.

Claim 93

Even if claim 10 is not allowable, Claim 93 is allowable as Yamaguchi does not teach administration to a site of inflammation.

Claim 96

Claim 96 is allowable as Yamaguchi does not teach administration to a subject having an autoimmune disease.

Claim 98

Claim 98 is allowable because Yamaguchi does not teach administration to a subject having an abscess, a transplant, an implant, atherosclerosis, or myocarditis.

Claim 100

Claim 100 is allowable because Yamaguchi does not teach hematopoietic progenitor cells.

Claim 105

Claim 105 is allowable because Yamaguchi does not teach the calcium-sensing receptor antagonist is N-[(R)-2-hydroxy-3-(2-cyano-3-chlorophenoxy) propyl]-1-dimethyl-2-(2-naphthyl) ethylamine (NPS-2143).

(d) Summary

Yamaguchi does not teach any of the limitations of the presently claimed invention and therefore cannot render the invention obvious. It does not teach inhibition of migration, the cell type specified by the claim, the activity in vivo nor the desirability to do so for any reason.

(8) Conclusion

Appellants request reversal of the rejection and allowance of the application.

Respectfully submitted,

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(10) CLAIMS APPENDIX

Claims listing:

This listing of claims will replace all prior versions, and listings, of claims in the application:

1-9. (Canceled)

10. (Previously Amended) A method of inhibiting migration of calcium-sensing receptor expressing hematopoietic cells to a specific site in a subject, comprising: locally administering to a specific site in a subject in need of such treatment a calcium-sensing receptor antagonist in an amount effective to inhibit migration of calcium-sensing receptor expressing hematopoietic cells to the specific site in the subject.

11-92. (Canceled)

93. (Previously Presented) The method of claim 10, wherein the specific site is a site of inflammation.

94. (Previously Presented) The method of claim 93, further comprising co-administration of a non-calcium-sensing receptor antagonist that inhibits migration of immune cells to the site of inflammation in the subject.

95. (Previously Presented) The method of claim 94, wherein the non-calcium-sensing receptor antagonist is an antiinflammatory agent.

96. (Previously Presented) The method of claim 10, wherein the subject has an autoimmune disease.

97. (Previously Presented) The method of claim 96, wherein the autoimmune disease is rheumatoid arthritis, uveitis, insulin-dependent diabetes mellitus, hemolytic anemias, rheumatic fever, Crohn's disease, Guillain-Barre syndrome, psoriasis, thyroiditis, Graves'

disease, myasthenia gravis, glomerulonephritis, autoimmune hepatitis, or systemic lupus erythematosus.

98. (Previously Presented) The method of claim 10, wherein the subject has an abscess, a transplant, an implant, atherosclerosis, or myocarditis.

99. (Canceled)

100. (Previously Amended) the method of claim 98, wherein the hematopoietic cells are hematopoietic progenitor cells.

101-104. (Canceled)

105. (Previously Presented) The method according to any of the claims 10, 93, 98 and 100, wherein the calcium-sensing receptor antagonist is N-[(R)-2-hydroxy-3-(2-cyano-3-chlorophenoxy) propyl]-1-dimethyl-2-(2-napthyl) ethylamine (NPS-2143).